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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,466	02/02/2001	Burton G. Christensen	P-087-R	7142

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,466	CHRISTENSEN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 12/19/03, claims 17-18 have been amended. Claims 1-18 and 20 remain pending.

Applicants' arguments filed 12/19/03 have been considered and found not persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is asserted in the specification (page 109, line 17+) that the claimed compounds were "active" in certain in vivo tests. The only *in vivo* tests which are described are the "mouse septiciemia model" (page 108, line 15+), and the mouse "neutropenic thigh model" (page 108, line 27+). However, no data are presented, and it is not clear what the criteria are for a compound to be considered "active". The "neutropenic thigh model" is described only briefly in the specification (page 108, line 27+). Additional examples of the "neutropenic thigh model" can be found in each of the following references: Boylan Carole

J (*Antimicrobial Agents and Chemotherapy* **47** (5) 1700-6, 2003); Rocchetta H L (*Antimicrobial Agents and Chemotherapy* **45** (1) 129-37, 2001); Mouton J. W., (*Antimicrobial Agents and Chemotherapy* **43** (10) 2473-8, 1999). As is evident, some analysis of the data is required. It may be the case the skilled microbiologist would be able to determine an "ED_{50}" parameter. But the question is, what are the minimal criteria for a compound to be "active"....? It is apparent that some statistical analysis would be required, particularly for the case in which a quantity of (alleged) antibacterial agent selected is sufficiently low as to be just above the threshold to produce a result that is "statistically significant". As is known to the statistician of ordinary skill, it is not uncommon for artifacts in statistical analysis to occur. This matter is discussed in each of the following references:

Ludbrook (*Clinical and Experimental Pharmacology and Physiology* **28** (5-6) 488-92, 2001)

Bryant (*Pediatric Allergy and Immunology* 9 (3) 108-15, 1998)

Bezeau (*Journal of Clinical and Experimental Neuropsychology* 23 (3) 399-406, 2001)

Bolton (*Journal of Clinical Pharmacology* 38 (5) 408-12, 1998)

Willenheimer (*Progress in Cardiovascular Diseases* 44 (3) 155-67, 2001)

Chung (*Plastic and Reconstructive Surgery* 109 (1) 1-6, 2002)

Atkinson (*Chronobiology International* 18 (6) 1041-53, 2001).

Consider next the "mouse septiciemia model". Suppose that 10 mice are inoculated with *S. aureus,* and that these 10 mice are divided into two groups of 5 mice each, i.e., "group 1" and "group 2". Suppose that one of the claimed compounds is administered to the 5 mice in group 1, and that "vehicle" only is administered to the 5 mice in group 2. Suppose that the result of this is that 3 of mice in group 2 mice died, and 2 lived, and that 3 of the mice in group 1 lived and 2 died. A person who's knowledge and experience is such as to place him below the level of the ordinarily skilled statistician might well believe that such an experimental result would be conclusive with regard to antibacterial activity. However, to the statistician of ordinary skill, such a result would not be meaningful.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, structure/activity relationships of antibacterial compounds are unpredictable. Consider, for example, the following:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline

systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.

- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.

- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori.*

- Goldman, R. C. (*FEMS Microbiology Letters* **183**(2), 209-214, 2000) discloses (sentence bridging pages 210-211) that removal of an amino acid from a vancomycin eliminates activity.

- Harris, Constance (*Journal of Antibiotics* **38**(1), 51-7, 1985) discloses that replacement of an asparagine residue in vancomycin with isoaspartic acid eliminates activity.

These and other references disclose that there do exist compounds which exhibit no antibacterial activity, and many of these inactive compounds are structurally analogous to compounds that <u>are</u> active. The key point is that the factors which give rise to activity or

inactivity are unknown in the art; and certainly the specification has made no attempt to discuss such factors. Accordingly, the skilled microbiologist cannot predict antibacterial activity merely by viewing a structure

It remains the case that "undue experimentation" would be required to determine which, if any, of the claimed compounds can exhibit antibacterial activity.

The response filed 12/19/03 presents several arguments, beginning with the assertion that methods of determining whether or not a given compound can inhibit growth of bacteria are known to the skilled microbiologist. This particular point is correct. The response also argues that NCCLS publishes procedures for determining MIC's for test compounds. It may be the case that NCCLS publishes procedures for determining the MIC's of compounds which are in fact inhibitors of bacterial propagation, but there is no evidence that the NCCLS publishes procedures for determining the MIC's of compounds which are inactive.

There is no evidence of record to refute the proposition that the claimed compounds are inactive, and if the compounds are in fact inactive, no procedure of the NCCLS will be useful to demonstrate activity.

The response also argues that the specification provides direction which enables the skilled microbiologist to use the claimed compounds to inhibit growth of bacteria. The specification does provide (page 106) a general guideline to a microbiologist who might endeavor to undertake *in vitro* tests. There is no assertion, however, that the compounds

exhibited efficacy *in vitro*. The only *in vivo* tests which are described are the "mouse septiciemia model" (page 108, line 15+), and the mouse "neutropenic thigh model" (page 108, line 27+). Page 21, paragraph 1 (response filed 12/19/03) ends with the conclusion that a skilled microbiologist could determine "whether a test compound exhibits antibacterial properties". The examiner is actually in agreement with this particular statement. But the key word is "whether", i.e., if a skilled microbiologist is presented with a compound which fails to inhibit growth of bacteria, he would be able to determine whether or not the compound fails to inhibit growth of bacteria. But the fact that he may be competent to undertake assays does not mean that the tested compounds will indeed inhibit growth of bacteria.

Next, the response argues (page 21) that the specification contains "working examples for determining [whether or not the compounds are active]". However, a proposed assay is not a working example. If a skilled microbiologist conducts a series of tests on a compound, and all tests results are negative, that does not amount to a "working example".

Next, the response argues that the claims are drawn to compounds, not to assay methods. This particular point is correct. The response also argues that because the relevant assay methods are routine, undue experimentation would not be required to practice the invention. However, the invention is that of compounds which are speculated to inhibit growth of bacteria. If the compounds do not in fact inhibit growth of bacteria, then it

would follow therefrom that the specification does not teach the skilled microbiologist how to "make and use" the compounds as required by 35 USC §112, first paragraph . If the arguments in the response were taken to their logical conclusion, it would follow that because antibacterial assays are routine, it is impossible to create a genus of compounds for which undue experimentation would be required, i.e., it is impossible for any genus of compounds not to contain at least some compounds which inhibit bacterial growth. However, this is not a reasonable conclusion; clearly compounds do exist which fail to inhibit growth of bacteria.

Next, the response argues that undue experimentation is not required because a PhD in microbiology is highly trained. It is agreed that a PhD in microbiology is highly trained. But that does not mean that there are no insolvable problems in microbiology; in particular, if a highly skilled microbiologist is presented with a compound which does not inhibit growth of bacteria, no amount of experience or education will be sufficient to make the compound inhibit growth of bacteria.

Next, the response argues that "the assays used... are highly predictable". This particular point is factually incorrect, and no evidence to support it has been presented. The response also argues that the results obtained by one skilled artisan can be reproduced by another skilled artisan using standard assays. This particular point may or may not be true, but it is true, at least in principle, that if two skilled microbiologists are following the

identical assay, similar results should be obtained. However, the degree of reproducibility is at most a secondary issue. The primary issue is that of predictability. With regard to this issue (predictability), the response argues that the examiner has provided no evidence to support the conclusion that the claimed compounds will fail to inhibit growth of bacteria. However, there is no statute or court decision which imposes such a high burden on the PTO; i.e., no court has ever stated that an enablement rejection is only sustainable if the PTO (or other relevant party) provides evidence that the claimed invention will fail to "work" under any and all circumstances. Moreover, the response provides no authority for the argument that the examiner should provide evidence that the claimed compounds will fail to inhibit growth of any and all bacteria. As acknowledged on pages 21-22 of the response, In re Wands has endorsed the principle of "unpredictability" as being a key factor to weigh in assessing the need (or absence thereof) for undue experimentation. As such, the issue is whether one can predict the propensity of a compound to inhibit growth of bacteria merely by viewing its structure. The response also argues that it is possible that some of the compounds within the claimed genus may be inactive, but that if that is true, the overall genus is still enabled. However, the issue is not whether 1% or 10% of the claimed compounds are inactive; instead the primary issue is whether any of the claimed compounds are active. Based on the record thus far, there is no reason to believe that the claimed compounds will inhibit growth of bacteria.

Given the absence of guidance as to how to use the compounds, the absence of working examples, the nature of the invention, the state of the prior art, the relative skill of microbiologists, and the unpredictability of structure/ activity relationships, the skilled artisan would conclude that "undue experimentation" would be required to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

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No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton

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